SYNTHESIS OF NICOTIANAMINE AND A RELATED COMPOUND, DERIVATIVES OF AZETIDINE-2-CARBOXYLIC ACID

Shinji Fushiya, Shuichi Nakatsuyama, Yoshikazu Sato, and Shigeo Nozoe*
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Abstract — The synthesis of nicotianamine (1) and a related compound (2) — amino acid derivatives having the azetidine ring — was achieved by reductive coupling of L-aspartic-ß-semialdehyde derivatives with L-azetidine-2-carboxylic acid methyl ester.

Nicotianamine (1) is a unique amino acid containing the azetidine-2-carboxylic acid moiety, first isolated from the leaves of Nicotiana tabacum. Its structure was elucidated as 2(S), 3'(S),3''(S)-N-[N-(3-amino-3-carboxypropyl)-3-amino-3-carboxypropyl]-azetidine-2-carboxylic acid by spectral analysis and by the chemical transformation from L-azetidine-2-carboxylic acid (AZC) (13). Nicotianamine (1) has also been found in many species of Solanaceae and some other plants. In spite of the wide distribution, the biological significance of this compound is still uncertain.

On the other hand, several amino acid derivatives related to nicotianamine (1) such as mugineic acid (3), mugineic acid A (4) and avenic acid A (5) have been isolated from the excreta of the roots of oats cultured under iron deficient conditions. These acidic amino acids possess an iron chelating activity and play a role in iron uptake and transport. During the course of our attempts to isolate such chelating amino acid derivatives, avenic acid B (5) was isolated from the root extract.

\[ \text{Nicotianamine (1)} \]
\[ \text{Mugineic acid (3)} \]
\[ \text{Avenic acid A (4)} \]
\[ \text{Avenic acid B (5)} \]
of *Avena sativa*. In our last paper, 8) we described the synthesis of this compound via reductive coupling of *L*-malic semi-aldehyde derivative 6 with *L*-homoserine lactone 7 by using NaBH₃CN, a selective reducing agent. It is thought that other chelating amino acids and related compounds, in which two or three molecules are connected through a C-N bond, can be synthesized as optically active forms by the same method. In the present communication, we describe the synthesis of nicotianamine (1) and *A2C* dimer (2), 2(S),3'(5)′-(3-amino-3-carboxypropyl)-azetidine-2-carboxylic acid isolated from the seeds of *Fagus silvatica* L. along with nicotianamine (1). 2)

The synthesis of 2 was achieved through reductive coupling of *L*-aspartic-8-semialdehyde derivative 13a to *A2C* methyl ester 14 by using NaBH₃CN after deprotection and, in the case of 1 two moles of aldehydes (12b and 12c) were combined stepwise with 12. 9) Since *L*-aspartic-8-semialdehyde is an important biogenetic precursor of *L*-homoserine and *L*-methionine, this compound might be a unit in the biosynthesis of nicotianamine (1), iron chelating amino acids and other C-4 amino acid derivatives. The requisite aldehydes 12a-c were synthesized in a fair yield from *L*-allylglycine 8 according to the method of Neuberger 10) with a modification. Treatment of *L*-allylglycine 8 with carbenzoxy chloride, followed by esterification with a) diazomethane b) Meerwein reagent and c) isobutylene gave corresponding esters 10a-c. Osmium tetroxide oxidation of the esters 10a-c afforded diols 11a-c, which were oxidized with sodium metaperiodate yielding corresponding aldehydes 12a-c: [α]D +29.9°, +19.7° and +15.1° (CHCl₃), respectively. The signals due to the aldehyde protons were observed at 9.68-9.73 ppm in the pmr spectra of the aldehydes 12a-c.
In preference to the synthesis, an authentic sample of nicotianamine (1) was isolated from young leaves of Lycium chinense.\(^3\) The spectral data of isolated \(1\) (mp 243\(^\circ\) (decom.), \([\alpha]_D -48.0^\circ\) (c=0.2, \(H_2O\)) were shown to be identical with those in the literature.\(^1,2\) Reaction of the aldehyde \(12a\) and 2\(\alpha\)C methylester \(14\) with \(NaBH_3CN\) at pH 6.0 afforded \(15a\) in a 62% yield: \([\alpha]_D -60.5^\circ\) (c=0.5, \(CHC{l}_3\)); \(ms, m/e 364.1658\) (calc'd for \(C_{18}H_{24}N_2O_6, 364.1635\)); ir \((CHC{l}_3) 1720, 1495, 1225,\) 1045 cm\(^{-1}\); pmr \((CDCl_3) \delta 7.33 (5H, s, -C{\_}H_5), 6.47 (1H, d, J=8, -NH), 5.12 (2H, s, OCH_2C_6H_5), 4.38 (1H, m, C(3')H), 3.69, 3.72 (each 3H, s, -OCH_3), 3.60 (1H, t, J=8, C(2)H), 3.39 (1H, m, C(4)H), 2.80 (1H, m, C(4)Hb), 2.4-2.9 (2H, m, C(1)H), 2.1-2.4 (2H, m, C(3)H), 1.6-2.0 (2H, m, C(2)H). In the case of \(12b\) and \(14\), \(15b\) was obtained in a 68% yield: \([\alpha]_D -78.0^\circ\) (c=0.1, \(CHC{l}_3\)). Deprotection of \(15a\): 1. \(H_2/10\%\) palladium carbon, 2. 1% methanolic potassium hydroxide, followed by chromatographic purification on a Dowex 50W column afforded the compound \(2\): \([\alpha]_D -81.8^\circ\) (c= 0.06, \(H_2O\)). The paper chromatography Rf value, \([\alpha]_D\) and the pmr spectrum of the synthetic specimen of \(2\) were shown to be identical with those of the natural one in the literature.\(^2\)
Reaction of the aldehyde 12a with 16a, the decarboxybenzoxylization product of 15a in the presence of NaBH₃CN at pH 6.0 gave a lactam 17: [α]D -45.3° (c=0.2, CHCl₃), in a 56% yield. The expected 18 was obtained by reductive condensation of the aldehyde 12c to 16b in a 75% yield: [α]D -35.4° (c=0.1, CHCl₃); ms, m/e 535.2909 (calc'd for C₂₇H₄₁N₃O₈, 535.2893); ir (CHC₁₃) 1720, 1500, 1367, 1230, 1150 cm⁻¹; pmr (CDCl₃) 6 7.32 (5H, s, -C₆H₅), 6.19 (1H, d, J=8, -NH), 5.08 (2H, s, 0-CH₂-C₆H₅), 4.15 (2H, q, J=7, 0-CH₂CH₃), 4.2-4.3 (1H, m, C(3,4)H), 3.66 (3H, s, -OCH₃), 3.2-3.7 (3H, m, C(2,3)H, C(3,5)H, C(4,6)H), 2.0-2.9 (7H, m, C(4)H, C(1,4)H₂, C(1,5)H₂, C(3,6)H₂), 1.25 (3H, t, J=7, -CH₂CH₃), 1.45 (9H, s, -C(CH₃)₃), 1.5-2.0 (4H, m, C(1,5)H₂, C(2,6)H₂). Deprotection of 18: 1. H₂/10% palladium carbon, 2. trifluoroacetic acid, 3. 1% potassium hydroxide, followed by chromatographic purification on a Dowex 50W column furnished the compound 1: mp 247° (decom.), [α]D -45.8° (c=0.1, H₂O). The specimen of synthetic 1 was shown to be identical with natural nicotianamine in all respects including the paper chromatography Rf value, Rt on HPLC and pmr spectrum. Further the synthetic 1 showed no melting point depression in the mixed mp test with natural nicotianamine.

As mentioned above, the optically active nicotianamine (1) and A2C dimer (2) were synthesized by reductive coupling of A2C methyl ester 14 and aspartic-β-semialdehyde derivatives 12a-c and, the synthesis of the chelating amino acid derivatives and related compounds by the same method is now under investigation.

REFERENCES AND NOTES
8. Submitted for publication
9. Satisfactory spectral data (pmr, ms and ir) were obtained for all intermediates.

Cordially dedicated to Professor Tetsuji Kametani on the occasion of his retirement from the Pharmaceutical Institute of Tohoku University.

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